

59. A DNA construct which alters the expression of a targeted gene in a cell when the DNA construct is homologously recombined with a target site within the chromosomal DNA of the cell, the target site being upstream of the endogenous ATG initiation codon of the targeted gene, the DNA construct comprising:

- (a) a targeting sequence homologous to the target site;
- (b) an exogenous regulatory sequence;
- (c) an exon; and
- (d) an unpaired splice-donor site.

60. A method comprising the steps of:

- (a) providing a DNA construct comprising:
  - (i) a targeting sequence;
  - (ii) an exogenous regulatory sequence;
  - (iii) an exon; and
  - (iv) an unpaired splice-donor site at the 3' end of the exon,
- (b) providing a cell, the genome of which comprises
  - (i) a target site homologous to the targeting sequence, and
  - (ii) a targeted endogenous gene having an endogenous regulatory region;
- (c) transfecting the cell with the DNA construct, thereby producing a transfected cell;

(d) maintaining the transfected cell under conditions appropriate for homologous recombination, thereby producing a homologously recombinant cell containing the exogenous regulatory sequence, the exon, and the splice-donor site, all operatively linked to the targeted endogenous gene in the cell's genome such that the exogenous regulatory sequence controls expression of the targeted gene to produce a transcript comprising RNA corresponding to the exon and unpaired splice-donor site, wherein the RNA corresponding to the unpaired splice-donor site of the transcript directs splicing to a splice-acceptor site of the transcript which directs splicing to a splice-acceptor site in the transcript which corresponds to a site within the targeted gene; and

(e) maintaining the homologously recombinant cell under conditions appropriate for transcription under the control of the exogenous regulatory sequence, to produce a transcript of the exon, the targeted gene, and any sequences lying between the exon and the targeted gene.

61. A method comprising the steps of:

- (a) providing a cell, the genome of which comprises
  - (i) a targeted endogenous gene having an endogenous regulatory region;
  - (ii) a target site upstream of the endogenous ATG initiation codon of a targeted gene; and
- (b) providing a DNA construct comprising:

(i) a targeting sequence homologous to the target site;

(ii) an exogenous regulatory sequence;

(iii) an exon; and

(iv) an unpaired splice-donor site,

wherein (i), (ii), (iii), and (iv) are oriented such that, upon homologous recombination of the targeting sequence with the target site, the exogenous regulatory sequence controls expression of the targeted gene to produce a transcript comprising RNA corresponding to the exon and unpaired splice-donor site, wherein the RNA corresponding to the unpaired splice-donor site of the transcript directs splicing to a splice-acceptor site of the transcript which corresponds to a site within the targeted gene;

(c) transfecting the cell with the DNA construct, thereby producing a transfected cell;

(d) maintaining the transfected cell under conditions appropriate for homologous recombination, thereby producing a homologously recombinant cell containing the exogenous regulatory sequence, the exon, and the unpaired splice-donor site, all operatively linked to the targeted gene; and

(e) maintaining the homologously recombinant cell under conditions appropriate for transcription under the control of the exogenous regulatory sequence, to produce a transcript of the exon, the targeted gene, and any sequence lying between the exon and the targeted gene.

62. A homologously recombinant cell having incorporated therein a new transcription unit, wherein the new transcription unit comprises an exogenous regulatory sequence, an exogenous exon, and a splice-donor site at the 3' end of the exogenous exon, the splice-donor site being operatively linked to the endogenous splice-acceptor site of what prior to homologous recombination was the second exon of an endogenous gene.

63. A homologously recombinant cell having incorporated therein a new transcription unit, wherein the new transcription unit comprises an exogenous regulatory sequence, an exogenous exon and a splice-donor site at the 3' end of the exogenous exon, all located upstream of an endogenous regulatory sequence of a targeted endogenous gene in a chromosome of the cell, the splice-donor site being operatively linked to the endogenous splice-acceptor site of what prior to homologous recombination was the second exon of the endogenous gene.

64. A DNA construct which alters the expression of an endogenous targeted gene in a cell when the DNA construct is homologously recombined with a target site within the chromosomal DNA of the cell, the target site being upstream of the endogenous ATG initiation codon of the endogenous targeted gene, the DNA construct comprising:

(a) a targeting sequence homologous to the target site;

(b) an exogenous regulatory sequence;

- (c) an exon;
- (d) a splice-donor site;
- (e) an intron; and
- (f) a splice-acceptor site;

wherein upon homologous recombination, (b)-(f) are operatively linked to the endogenous targeted gene.

65. A method of providing a therapeutic product to a mammal, comprising introducing into the mammal a vertebrate cell which produces the therapeutic product, the cell being generated by a process comprising:

- (a) providing a vertebrate cell the genomic DNA of which comprises an endogenous gene encoding the therapeutic product;

- (b) providing a DNA construct comprising:

- (1) a targeting sequence homologous to a target site within or upstream of the endogenous gene,
  - (2) an exogenous regulatory sequence,
  - (3) an exon, and
  - (4) an unpaired splice-donor site at the 3' end of the exon; and

- (c) transfecting the vertebrate cell with the DNA molecule, thereby generating a homologously recombinant cell in which the exogenous regulatory sequence is operatively linked to the endogenous gene and thereby permits the transcription of the exon, the endogenous gene, and any sequences lying between the exon and the endogenous gene, said transcription being under the